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(54) Thiazole compounds, processes for the preparation thereof, and pharmaceutical composition comprising the same.

(57) The present invention relates to new thiazole compounds and pharmaceutically acceptable salts thereof which have pharmacological activities, processes for preparation thereof, a pharmaceutical composition comprising the same same and a use of the same.

EP 0 377 457 A1

THIAZOLE COMPOUNDS, PROCESSES FOR THE PREPARATION THEREOF AND PHARMACEUTICAL COMPOSITION COMPRISING THE SAME

This invention relates to new thiazole compounds. More particularly, this invention relates to new thiazole compounds and pharmaceutically acceptable salts thereof which have pharmacological activities, processes for preparation thereof, a pharmaceutical composition comprising the same and a use of the same.

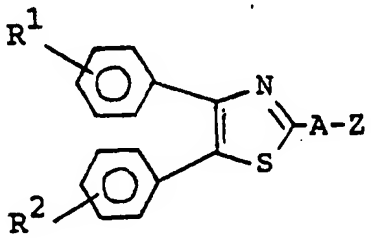
Accordingly, one object of this invention is to provide the new and useful thiazole compounds and pharmaceutically acceptable salts thereof which possess antithrombotic, vasodilating,antiallergic, anti-inflammatory and 5-lipoxygenase inhibitory activities.

Another object of this invention is to provide processes for preparation of the thiazole compounds and salt thereof.

A further object of this invention is to provide a pharmaceutical composition comprising said thiazole compounds or a pharmaceutically acceptable salt thereof.

Still further object of this invention is to provide a use of said thiazole compound or a pharmaceutically acceptable salts thereof as a medicament for prophylactic and therapeutic treatment of thrombosis, hypertension, cardiovascular or cerebrovascular diseases, allergy and inflammation, particularly thrombosis, in human being and animals.

The object thiazole compounds of the present invention are novel and represented by the following general formula :



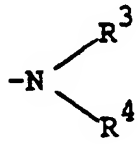
(I)

wherein

R^1 and R^2 are each halogen, lower alkyloxy, lower alkylthio or lower alkylsulfinyl,

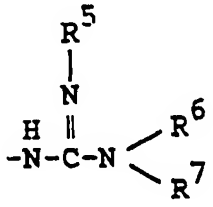
A is lower alkylene, carbonyl or single bond, and

Z is heterocyclic group which may have suitable substituent(s), a group of the formula :



in which R^3 and R^4 are each hydrogen, lower alkyl which may have heterocyclic group or piperidyl which may have suitable substituent(s),

or a group of the formula :

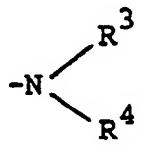


in which

(1) R^5, R^6 and R^7 are each hydrogen, lower alkyl or cyclo(lower)alkyl;

(2) R^5 is hydrogen, lower alkyl, or cyclo(lower)alkyl, and
R^6 and R^7 are linked together with the attached nitrogen atom to form heterocyclic group which may have suitable substituent(s); or

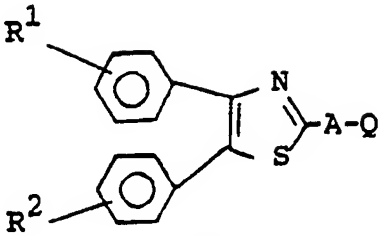
(3) R^5 and R^6 are linked together to form lower alkylene, and
R^7 is hydrogen; provided that when Z is a group of the formula :



wherein R^3 and R^4 are each as defined above, then A is lower alkylene or carbonyl.

The object compound (I) of the present invention can be prepared by the following processes.

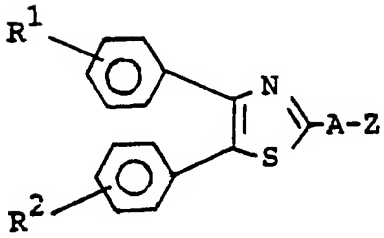
Process (a)



(II)

H-Z (III)

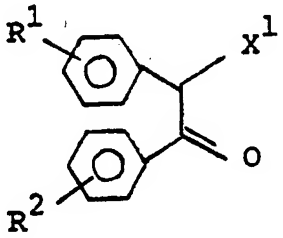
or a salt thereof



(I)

or a salt thereof

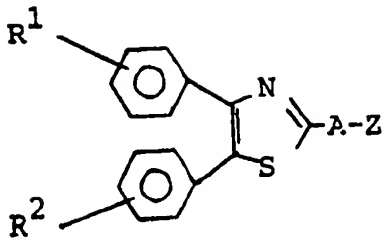
Process (b)



(IV)

$H_2N-\overset{\overset{S}{\|}}{C}-A-Z$ (V)

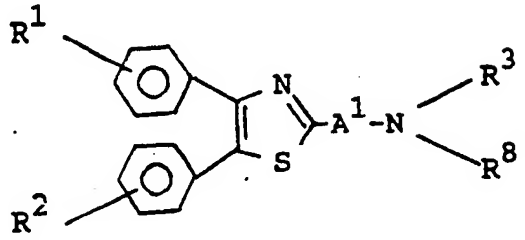
or a salt thereof



(I)

or a salt thereof

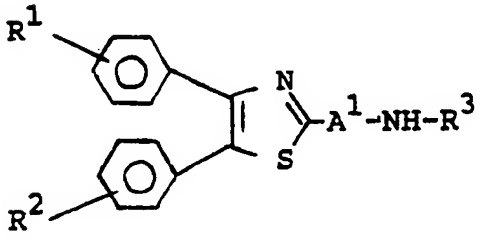
Process (c)



(VI)

or a salt thereof

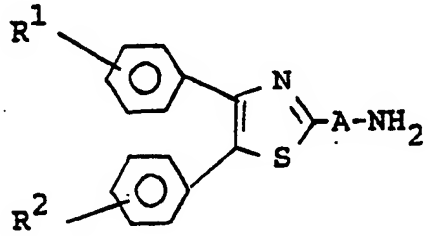
elimination reaction of the amino-protective group on R^8



(Ia)

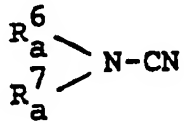
or a salt thereof

Process (d)

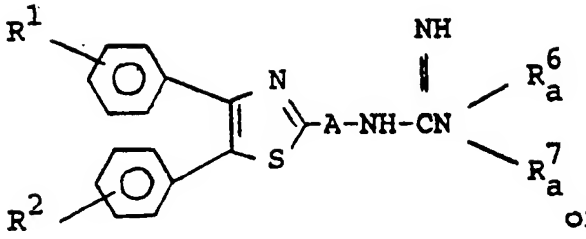


(Ib)

or a salt thereof



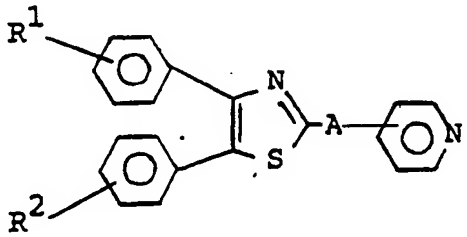
(VII)



(Ic)

or a salt thereof

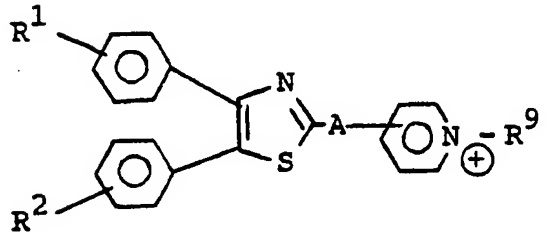
Process (e)



(Id)

or a salt thereof

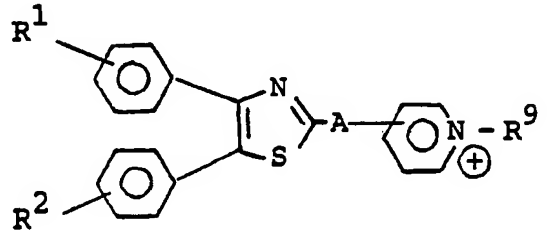
X^2-R^9 (VIII)



(Ie)

or a salt thereof

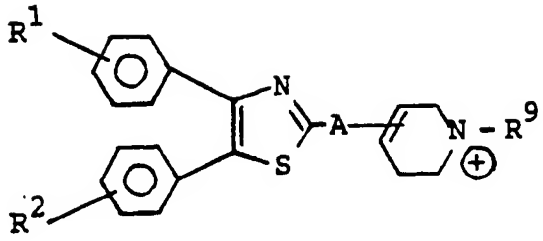
Process (f)



(Ie)

or a salt thereof

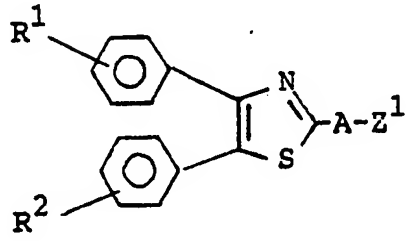
reduction



(If)

or a salt thereof

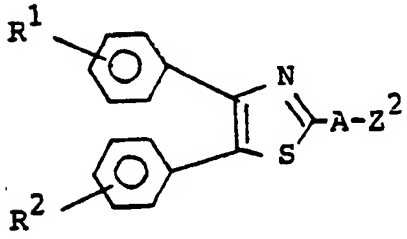
Process (g)



(Ig)

or a salt thereof

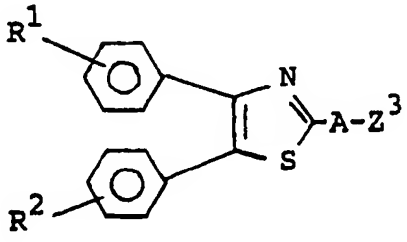
oxidation



(Ih)

or a salt thereof

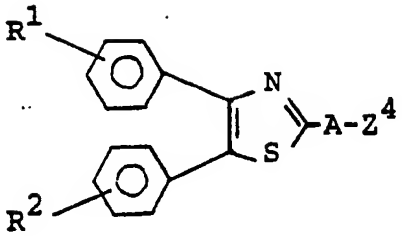
Process (h)



(Ii)

or a salt thereof

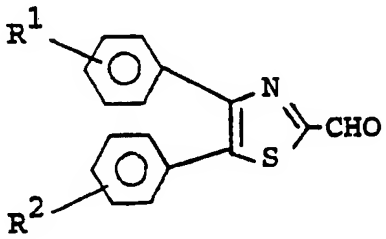
acylating reaction



(Ij)

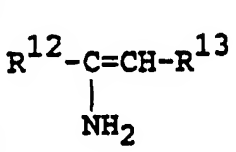
or a salt thereof

Process (i)

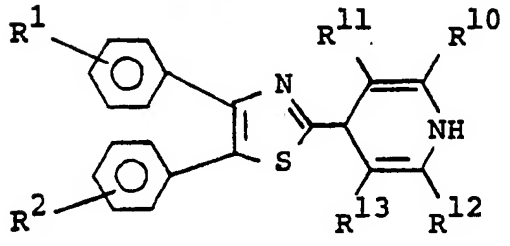


(IX)

R^{10}-CO-CH_2-R^{11} (X), and



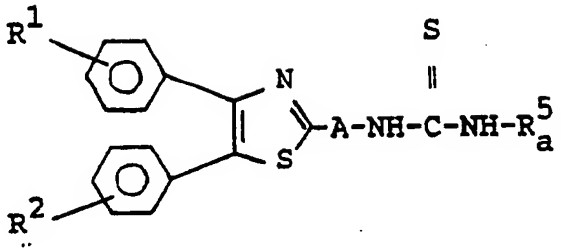
(XI)



(Ik)

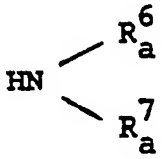
or a salt thereof

Process (j)



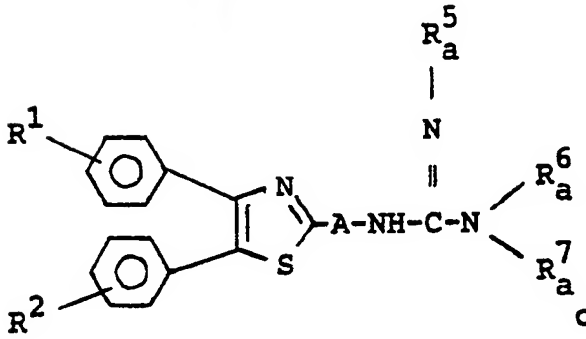
(XII)

or a salt thereof



(XIII)

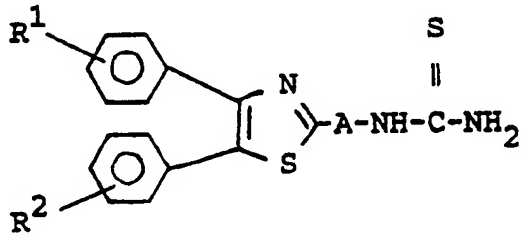
or a salt thereof



(Iℓ)

or a salt thereof

Process (k)

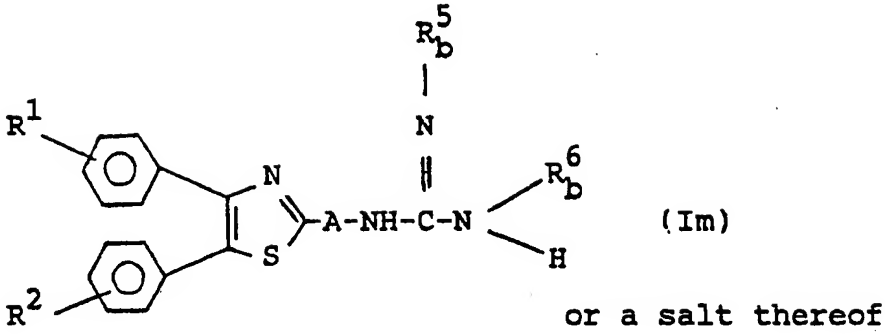


(XIV)

or a salt thereof

lower alkylenediamine

or a salt thereof



(Im)

or a salt thereof

wherein

R^1, R^2, R^3, A and Z are each as defined above,

R_a^5, R_a^6 and R_a^7 are each hydrogen, lower alkyl or cyclo(lower)alkyl, or

R_a^6 and R_a^7 are linked together with the attached nitrogen atom to form heterocyclic group which may have suitable substituent(s),

R_b^5 and R_b^6 are linked together to form lower alkylene,

R^8 is amino-protective group,

R^9, R^{10} and R^{12} are each lower alkyl,

R^{11} and R^{13} are each carboxy or a protected carboxy group,

A^1 is lower alkylene or carbonyl,

Q is a suitable leaving group,

X^1 and X^2 are each an acid residue,

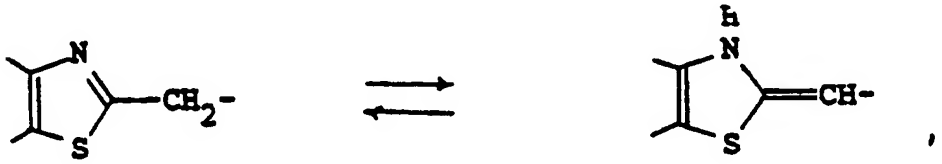
Z^1 is heterocyclic group having at least one nitrogen or one sulfur atom in its cyclic ring,

Z^2 is heterocyclic group having at least one oxidized nitrogen or one oxidized sulfur atom in its cyclic ring,

Z^3 is heterocyclic group having an imino moiety in its cyclic ring, and

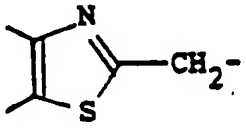
Z^4 is heterocyclic group having acylimino moiety in its cyclic ring.

In the present invention, with regard to the object compound (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (Il) and (Im) and the starting compound (II), (VI), (XII) and (XIV) and when A or A^1 is lower alkylene, it is to be understood that there may be tautomeric equilibrium between the partial structures of such compound as follows.



and such tautomer is also included within the scope of the present invention.

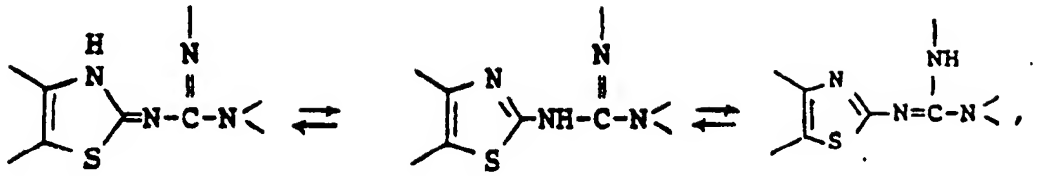
However, in the present invention, the partial structure of the compounds (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (Il), (Im), (II), (VI), (XII and (XIV) in case A or A^1 is lower alkylene, are represented by the following one expression for convenient sake,



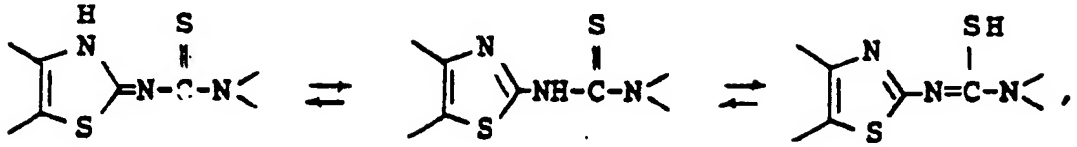
and the compounds (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (Il), (Im), (II), (VI) and (XIV) are named on the basis of such formula, when A or A^1 is lower alkylene.

And, with regard to the object compound (I), (Ic), (Il) and (Im) and the starting compounds (II), (XII) and (XIV), it is to be understood that there may be tautomeric equilibrium between the partial structures of such

compounds as follows.

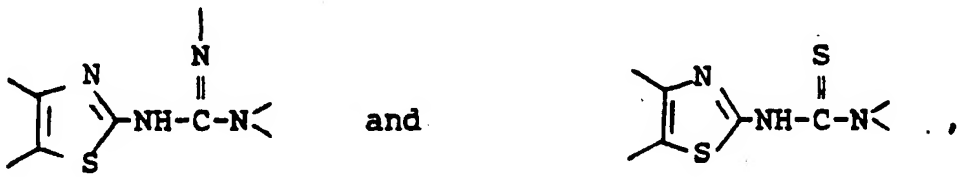


and



and
these tautomers are also included within the scope of the present invention.

However, in the present invention, the partial structure of the compounds (I), (Ic), (Iℓ), (Im), (II), (XII) and (XIV) are represented by one expression for convenient sake, that is by the following formulae :



and the compounds (I), (Ic), (Iℓ), (Im), (II), (XII) and (XIV) are named on the basis of such formulae.

Suitable pharmaceutically acceptable salts of the object compounds (I), (Ia), (Ib), (Ic), (Id), (If), (Ih), (Ii), (Ij), (Ik), (Iℓ) or (Im) are conventional non-toxic salts and may include e.g. a salt with a base or an acid addition salt such as a salt with an inorganic base, for example, an alkali metal salt (e.g. sodium salt, potassium salt, etc.), an alkaline earth metal salt (e.g. calcium salt, magnesium salt, etc.) an ammonium salt; a salt with an organic base, for example, an organic amine salt, (e.g. triethylamine salt, pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt, dicyclohexylamine salt, N,N′-dibenzylethylenediamine salt, etc.); an inorganic acid addition salt (e.g. hydrochloride, hydrobromide, sulfate, phosphate, etc.); an organic carboxylic or sulfonic acid addition salt (e.g. formate, acetate, trifluoroacetate, maleate, tartrate, methanesulfonate, benzenesulfonate, toluenesulfonate, etc.); a salt with a basic or acidic amino acid (e.g. arginine, aspartic acid, glutamic acid, etc.).

In the above and subsequent descriptions of the present specification, suitable examples and illustration of the various definitions which the present invention intends to include within the scope thereof are explained in detail as follows.

The term "lower" is used to intend a group having 1 to 6, preferably 1 to 4, carbon atom(s), unless otherwise provided.

Suitable "lower alkyl" and lower alkyl moiety in the term "lower alkyloxy", "lower alkylthio", "lower alkylsulfinyl" and "lower alkyl which may have heterocyclic group" may include straight or branched one having 1 to 6 carbon atom(s), such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, tert-pentyl, hexyl, and the like, preferably one having 1 to 4 carbon atom(s).

Suitable "lower alkylene" may be straight or branched one having 1 to 6 carbon atom(s), such as methylene, ethylene, trimethylene, propylene, tetramethylene, pentamethylene, hexamethylene, and the like, preferably one having 1 to 4 carbon atom(s), and the most preferably methylene.

Suitable "cyclo(lower)alkyl" may include 3 to 8 membered cycloalkyl such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and the like, preferably one having 5 to 7 carbon atoms.

Suitable "halogen" may be fluorine, chlorine, bromine or iodine.

Suitable "heterocyclic group" in "heterocyclic group which may have suitable substituent(s)" and "lower alkyl which may have heterocyclic group" may be aliphatic or aromatic, heteromonocyclic or heteropolycyclic group containing at least one hetero atom such as nitrogen, oxygen and sulfur atoms, and more suitable "heterocyclic group" thus defined may include 5 to 7 membered aliphatic heteromonocyclic group having one to three hetero atom(s) selected from nitrogen, oxygen and sulfur or 5 to 6 membered aromatic heteromonocyclic group having one to three hetero atom(s) selected from nitrogen, oxygen and sulfur, such as piperidyl, piperazinyl, morpholinyl, thiomorpholinyl, pyridyl, dihydropyridyl, tetrahydropyridyl, perhydrodiazepinyl, tetrahydropyridazinyl, and the like.

Suitable substituent on such heterocyclic group and "piperidyl" may include amino; hydroxy; nitro; cyano; lower alkyl as exemplified above; lower alkoxy as exemplified above; hydroxy(lower)alkyl in which the lower alkyl moiety may be the same as those exemplified above; acyl(lower)alkyl, the acyl group of which may be the same as those exemplified below, preferably carbamoyl(lower)alkyl (e.g. carbamoylmethyl, carbamoylethyl, etc.), lower alkylcarbamoyl(lower)alkyl (e.g. methylcarbamoylmethyl, ethylcarbamoylmethyl, propylcarbamoylmethyl, isopropylcarbamoylmethyl, methylcarbamoylethyl, etc.); oxo; acyl as exemplified below, preferably lower alkylcarbamoyl (e.g. methylcarbamoyl, ethylcarbamoyl, propylcarbamoyl, isopropylcarbamoyl, butylcarbamoyl, hexylcarbamoyl, etc.), lower alkanoyl (e.g. formyl, acetyl, propionyl, butyryl, pentanoyl, hexanoyl, pivaloyl, etc.), etc.; protected amino such as acylamino, in which the acyl moiety may be the same as those exemplified below, preferably lower alkanoylamino (e.g. formylamino, acetylamino, propionylamino, butyrylamino, valerylamino, hexanoylamino, pivaloylamino, etc.); carboxy; protected carboxy such as esterified carboxy, for example lower alkoxycarbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, hexyloxycarbonyl, neopentyloxycarbonyl, etc.); ar(lower)alkyl such as mono or di or triphenyl(lower)alkyl (e.g. benzyl, benzhydryl, trityl, phenethyl, etc.); and the like.

Suitable examples of the said acyl may be aliphatic, aromatic acyl derived from carboxylic, carbonic, sulfonic and carbamic acid such as lower alkanoyl (e.g., formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, oxalyl, succinyl, pivaloyl, etc.), preferably one having 1 to 4 carbon atom(s), more preferably one having 1 to 2 carbon atom(s); lower alkoxycarbonyl having 2 to 7 carbon atoms (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, 1-cyclopropylethoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, t-butoxycarbonyl, pentyloxycarbonyl, t-pentyloxycarbonyl, hexyloxycarbonyl, etc.), preferably one having 3 to 6 carbon atoms;

lower alkanesulfonyl (e.g., mesyl, ethanesulfonyl, propanesulfonyl, isopropanesulfonyl, butanesulfonyl, etc.); arenesulfonyl (e.g., benzenesulfonyl, tosyl, etc.); aroyl (e.g., benzoyl, toluoyl, naphthoyl, phthaloyl, indancarbonyl, etc.);

ar(lower)alkanoyl (e.g. phenylacetyl, phenylpropionyl, etc.); cyclo(lower)alkyl(lower)alkanoyl (e.g. cyclohexylacetyl, cyclopentylacetyl, etc.);

ar(lower)alkoxycarbonyl (e.g. benzyloxycarbonyl, phenethyloxycarbonyl, etc.); and the like:

Suitable "leaving group" is a group which is capable of replacing with a group of the formula :

-Z

(wherein Z is as defined above), preferably halogen (e.g., fluorine, chlorine, bromine, iodine, etc.), acyloxy (e.g., acetoxy, methanesulfonyloxy, etc.) or lower alkyloxy which can be the same as described in the above.

Suitable "acid residue" may be halogen (e.g. chlorine, bromine, iodine or fluorine); acyloxy such as lower alkanoyloxy (e.g. acetoxy, etc.), lower alkanesulfonyloxy (e.g. methanesulfonyloxy, etc.), and the like, and preferably halogen.

Suitable "amino-protective group" may be acyl, which may be the same as described in the above.

Suitable "protected carboxy group" may be esterified carboxy group, which may be the same as described in the above.

Suitable acyl moiety of the "acylimino" in Z^4 may be the same as described in the above.

"Heterocyclic group which may have suitable substituent(s)" formed by linking together with the attached nitrogen atom for R^6 and R^7 or R^6_a and R^7_a may be the same as those explained above, in which the heterocyclic group has at least one nitrogen atom and the binding radical comes from the said nitrogen atom such as piperazin-1-yl, lower alkylpiperazin-1-yl, morpholino, thiomorpholino, and the like.

Suitable "heterocyclic group having at least one nitrogen or one sulfur atom in its cyclic ring" may be the same as the heterocyclic group as explained above, in which the heterocyclic group has at least one nitrogen atom or one sulfur atom such as piperazinyl (e.g. piperazin-1-yl, etc.), 4-lower alkylpirepazinyl (e.g. 4-methylpiperazin-1-yl, etc.), thiomorpholino, and the like.

Suitable "heterocyclic group having at least one oxidized nitrogen or one oxidized sulfur atom in its cyclic ring" may be the same as the heterocyclic group as explained above, in which the heterocyclic

group has at least one oxidized nitrogen atom or one oxidized sulfur atom such as 4-oxopiperazinyl (e.g. 4-oxopiperazin-1-yl, etc.), 4-lower alkyl-4-oxopiperazinyl (e.g. 4-methyl-4-oxoIrepazin-1-yl, etc.), 1-mono or 1,1-dioxothiomorpholino, and the like.

Suitable "heterocyclic group having an imino moiety in its cyclic ring" may be the same as those explained above, in which the heterocyclic group has an imino moiety such as piperazinyl (e.g. piperazin-1-yl, etc.), and the like.

Suitable "heterocyclic group having an acylimino moiety in its cyclic ring" may be the same as those explained above, in which the heterocyclic group has an imino moiety and the said imino moiety is substituted by acyl such as 4-lower alkanoylpiperazinyl (e.g. 4-acetylpiperazin-1-yl, etc.), lower alkylcarbamoyl (e.g. isopropylcarbamoyl, etc.), and the like.

Particularly, suitable examples of "heterocyclic group which may have suitable substituent(s)" in Z may be piperazinyl; lower alkylpiperazinyl (e.g. 4-methylpiperazin-1-yl, etc.); hydroxy(lower)alkylpiperazinyl [e.g. 4-(2-hydroxyethyl)piperazin-1-yl, etc.]; acylpiperazinyl such as lower alkanoylpiperazinyl (e.g. 4-acetylpiperazin-1-yl, etc.), lower alkylcarbamoylpiperazinyl (e.g. 4-isopropylcarbamoylpiperazin-1-yl, etc.), etc.; acyl(lower)alkylpiperazinyl such as lower alkylcarbamoyl(lower)alkylpiperazinyl (e.g. 4-isopropylcarbamoylmethylpiperazin-1-yl, etc.); lower alkyl and oxo-disubstituted piperazinyl (e.g. 4-methyl-4-oxopiperazin-1-yl, etc.); morpholinyl (e.g. morpholino, etc.); thiomorpholinyl (e.g. thiomorpholino, etc.); dioxothiomorpholinyl (e.g. 1,1-dioxothiomorpholino, etc.); piperidyl (e.g. piperidino, etc.); hydroxy(lower)-alkylpiperidyl [e.g. 2-(2-hydroxyethyl)piperidino, etc.); acylaminopiperidyl such as lower alkanoylaminopiperidyl (e.g. 4-acetylaminopiperidino, etc.), etc.; lower alkylperhydrodiazepinyl (e.g. 4-methyl-1,4-perhydrodiazepin-1-yl, etc.); pyridyl (e.g. 4-pyridyl, etc.); lower alkylpyridyl (e.g. 1-methyl-4-pyridyl, etc.); lower alkyltetrahydropyridyl (e.g. 1-methyl-1,2,5,6-tetrahydro-4-pyridyl, etc.); one or two protected carboxy and one or two lower alkyl-substituted dihydropyridine such as bis(lower alkyloxycarbonyl)-di-(lower)alkyldihydropyridyl [e.g. 3,5-bis(ethoxycarbonyl)-2,6-dimethyl-1,4-dihydro-4-pyridyl, etc.)etc.; or oxo-tetrahydropyridazinyl (e.g. 6-oxo-1,4,5,6-tetrahydropyridazin-3-yl, etc.).

And, suitable examples of "lower alkyl which may have heterocyclic group" in R^3 and/or R^4 may be morpholinyl(lower)alkyl (e.g. 2-morpholinoethyl, etc.), pyridyl(lower)alkyl [e.g. 2-(2-pyridyl)ethyl, etc.], and the like.

And, suitable examples of "piperidyl which may have suitable substituent(s)" may be ar(lower)-alkylpiperidyl such as mono or di or triphenyl(lower)alkylpiperidyl (e.g. 1-benzylpiperidin-4-yl, etc.), and the like.

The processes for preparing the object compound (I) are explained in detail in the following.

Process (a)

The object compound (I) or a salt thereof can be prepared by reacting the compound (II) with the compound (III) or a salt thereof.

Suitable salts of the compound (III) can be referred to the ones as exemplified for the compound (I).

The reaction is usually carried out in a conventional solvent such as alcohols (e.g. methanol, ethanol, ethylene glycol, etc.), chloroform, ether, tetrahydrofuran, benzene or any other organic solvent which does not adversely influence the reaction.

The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

The reaction may be also carried out in the presence of an inorganic or an organic base such as an alkali metal hydroxide, an alkali metal hydrogencarbonate, alkali metal carbonate, alkali metal acetate, tri-(lower)alkylamine, pyridine (e.g. pyridine, lutidine, picoline, dimethylaminopyridine, etc.), N-(lower)-alkylmorpholine, N,N-di(lower)alkylbenzylamine, N,N-di(lower)alkylaniline or the like. When the base and/or the starting compound are in liquid, they can be used also as a solvent.

Process (b)

The object compound (I) or a salt thereof can be prepared by reacting the compound (IV) with the compound (V) or a salt thereof.

Suitable salt of the compound (V) can be referred to the ones as exemplified for the compound (I).

The reaction is usually carried out in a conventional solvent such as water, alcohols (e.g., methanol, ethanol, isopropyl alcohol, etc.), tetrahydrofuran, dioxane, chloroform, methylene chloride, dimethyl acetamide, N,N-dimethylformamide or any other organic solvent which does not adversely influence the

reaction. Among these solvents, hydrophilic solvents may be used in a mixture with water.

The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

This reaction may also be carried out in the presence of an inorganic or an organic base as defined above in Process (a).

Process (c)

The compound (Ia) or a salt thereof can be prepared by subjecting the compound (VI) or a salt thereof to elimination reaction of the amino-protective group on R^8.

Suitable method for this elimination reaction may include conventional one such as hydrolysis.

Hydrolysis is preferably carried out in the presence of an acid or a base.

Suitable acid may be an inorganic acid (e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, etc.), an organic acid (e.g. formic acid, acetic acid, trifluoroacetic acid, propionic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, etc.), an acidic ion-exchange resin and the like. In case that the organic acid such as trifluoroacetic acid and p-toluenesulfonic acid is used in this reaction, the reaction is preferably carried out in the presence of cation trapping agents (e.g. anisole, etc.).

The acid suitable for this hydrolysis can be selected according to the kinds of the amino-protective group to be eliminated, for example, this hydrolysis can preferably be applied to the amino-protective group for R^8 such as lower alkoxycarbonyl or lower alkanoyl.

Suitable base may include an inorganic base and an organic base such as an alkali metal (e.g. sodium, potassium, etc.), an alkaline earth metal (e.g. magnesium, calcium, etc.), the hydroxide or carbonate or hydrogencarbonate thereof, trialkylamine (e.g. trimethylamine, triethylamine, etc.), picoline, 1,5-diazabicyclo-[4.3.0] none-5-ene, 1,4-diazabicyclo[2.2.2]octane, 1,8-diazabicyclo[5.4.0]undecene-7, or the like.

The hydrolysis is usually carried out in a conventional solvent which does not adversely influence the reaction such as water, methanol, ethanol, propanol, tert-butyl alcohol, tetrahydrofuran, N,N-dimethylformamide, dioxane or a mixture thereof, and further the above-mentioned acids can also be used as a solvent when they are in liquid.

The reaction temperature of this hydrolysis is not critical, and the reaction is usually carried out under cooling to heating.

Process (d)

The compound (Ic) or a salt thereof can be prepared by reacting the compound (Ib) or a salt thereof with the compound (VII).

The reaction is usually carried out in a conventional solvent such as water, alcohols (e.g., methanol, ethanol, isopropyl alcohol, etc.), tetrahydrofuran, dioxane, chloroform, methylene chloride, dimethyl acetamide, N,N-dimethylformamide or any other organic solvent which does not adversely influence the reaction. Among these solvents, hydrophilic solvents may be used in a mixture with water.

The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

Process (e)

The compound (Ie) or a salt thereof can be prepared by reacting the compound (Id) or a salt thereof with the compound (VIII).

The reaction is usually carried out in a conventional solvent such as water, alcohol (e.g., methanol, ethanol, isopropyl alcohol, etc.), tetrahydrofuran, dioxane, chloroform, methylene chloride, dimethyl acetamide, N,N-dimethylformamide or any other organic solvent which does not adversely influence the reaction. Among these solvents, hydrophilic solvents may be used in a mixture with water.

The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

Process (f)

The compound (If) or a salt thereof can be prepared by subjecting the compound (Ie) or a salt thereof to reduction.

Reduction is carried out in a conventional manner, which is capable of reducing a pyridine ring to a 1,2,5,6-tetrahydropyridine ring, including chemical reduction and catalytic reduction.

Suitable reducing agents to be used in chemical reduction are hydrides (e.g. hydrogen iodide, hydrogen sulfide, lithium aluminum hydride, sodium borohydride, etc.) or a combination of a metal (e.g. tin, zinc, iron, etc.) or metallic compound (e.g. chromium chloride, chromium acetate, etc.) and an organic or inorganic acid (e.g. formic acid, acetic acid, propionic acid, trifluoroacetic acid, p-toluenesulfonic acid, hydrochloric acid, hydrobromic acid, etc.).

Suitable catalysts to be used in catalytic reduction are conventional ones such as platinum catalysts (e.g. platinum plate, spongy platinum, platinum black, colloidal platinum, platinum oxide, platinum wire, etc.), palladium catalysts (e.g. spongy palladium, palladium black, palladium oxide, palladium on carbon, colloidal palladium, palladium on barium sulfate, palladium on barium carbonate, etc.), nickel catalysts (e.g. reduced nickel, nickel oxide, Raney nikel, etc.), cobalt catalysts (e.g. reduced cobalt, Raney cobalt, etc.), iron catalysts (e.g. reduced iron, Raney iron, etc.), copper catalysts (e.g. reduced copper, Raney copper, Ullman copper, etc.) and the like.

The reduction is usually carried out in a solvent such as water, alcohol (e.g. methanol, ethanol, etc.), N,N-dimethylformamide, tetrahydrofuran, a mixture thereof or any other solvent which does not adversely affect the reaction.

Additionally, in case that the above-mentioned acids to be used in chemical reduction are in liquid, they can also be used as a solvent.

The reaction temperature of this reduction is not critical and the reaction is usually carried out under cooling to warming.

Process (g)

The object compound (Ih) or a salt thereof can be prepared by subjecting the compound (Ig) or a salt thereof to oxidation reaction.

Oxidation is carried out in a conventional manner, which is capable of oxidizing a nitrogen and/or sulfur atom(s) to an oxidized nitrogen and/or oxidized sulfur atom(s), and suitable oxidizing reagent may be oxygen acid such as periodate (e.g. sodium periodate, etc.), peroxy acid such as peroxybenzoic acids (e.g. peroxybenzoic acid, m-chloroperoxybenzoic acid, etc.), and the like.

The reaction is usually carried out in a conventional solvent such as water, alcohol (e.g., methanol, ethanol, isopropyl alcohol, etc.), tetrahydrofuran, dioxane, dichloromethane, chloroform, dimethyl acetamide, N,N-dimethylformamide or any other organic solvent which does not adversely influence the reaction. Among these solvents, hydrophilic solvents may be used in a mixture with water.

The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

In this reaction, lower alkylthio group for R^1 and R^2 are simultaneously oxidized to lower alkylsulfinyl or lower alkylsulfonyl, and such case is also included within the scope of the present reaction.

Process (h)

The object compound (Ij) or a salt thereof can be prepared by subjecting the compound (Ii) or a salt thereof to an acylating reaction.

The acylating reaction is carried out in a conventional manner under the existence of a suitable acylating agent which is capable of converting an imino moiety to an acylimino moiety.

The acyl group introduced by the acylating agent can be referred to one explained before.

Suitable acylating agent may be carboxylic, carbonic, sulfonic and carbamic acid and their reactive derivative such as acid halide (e.g. acid chloride, etc.), acid anhydride; activated ester; substituted isocyanate, for example N-(lower)alkylisocyanate (e.g. N-isopropyl isocyanate, etc.), and the like.

The reaction is usually carried out in a conventional solvent such as alcohol (e.g., methanol, ethanol, isopropyl alcohol, etc.), tetrahydrofuran, dioxane, dichloromethane, chloroform, dimethyl acetamide, N,N-dimethylformamide or any other organic solvent which does not adversely influence the reaction.

The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

Process (i)

The object compound (Ik) or a salt thereof can be prepared by reacting the compound (IX) with the compounds (X) and (XI).

The reaction is usually carried out in a conventional solvent such as water, alcohols (e.g. methanol, ethanol, isopropyl alcohol, etc.), tetrahydrofuran, dioxane, chloroform, methylene chloride, dimethyl acetamide, N,N-dimethylformamide or any other organic solvent which does not adversely influence the reaction. Among these solvents, hydrophilic solvents may be used in a mixture with water.

The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

Process (j)

The object compound (Il) or a salt thereof can be prepared by reacting the compound (XII) with the compound (XIII) or a salt thereof.

Suitable salts of the compound (XIII) can be referred to the ones as exemplified for the compound (I).

The reaction may be carried out in the presence of activating agents such as lower alkyl halide (e.g., methyl iodide, etc.), ar(lower)alkyl halide (e.g. benzyl iodide, etc.), or the like, which is capable of activating a substitution reaction of thiocarbonyl group ($\rangle C=S$).

The reaction is usually carried out in a conventional solvent such as alcohol (e.g., methanol, ethanol, etc.), chloroform, ether, tetrahydrofuran, benzene or any other organic solvent which does not adversely influence the reaction.

The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

The reaction may be also carried out in the presence of an inorganic or an organic base such as an alkali metal hydroxide, an alkali metal hydrogencarbonate, alkali metal carbonate, alkali metal acetate, tri(lower)alkylamine, pyridine, N-(lower)alkylmorpholine, N,N-di(lower)alkylbenzylamine, N,N-di(lower)alkylaniline, or the like. When the base is in liquid, it can be used also as a solvent.

Process (k)

The compound (Im) or a salt thereof can be prepared by reacting the compound (XIV) with lower alkylenediamine or a salt thereof.

Suitable salts of lower alkylenediamine can be referred to the ones as exemplified for the compound (I).

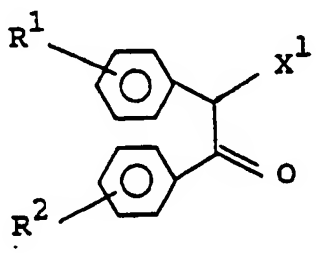
This reaction can be carried out by substantially the same method as that illustrated for Process (j), and therefore reaction conditions (i.e. reaction temperature and solvent, etc.) are to be referred to said explanation.

The object compounds (I), (Ia), (Ib), (Ic), (Ie), (If), (Ih), (Ij), (Ik), (Il) and (Im) obtained by the above processes or salts thereof can be isolated and purified by using conventional manners in this field, such as column chromatography, recrystallization, or the like.

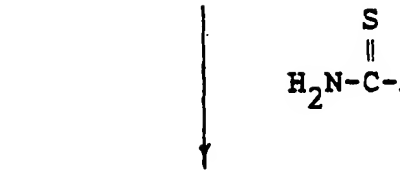
The compounds (I) may be converted into the aforesaid salts according to a conventional manner.

Some of the starting compounds in Process (a) to (k) are novel and can be prepared by the following processes.

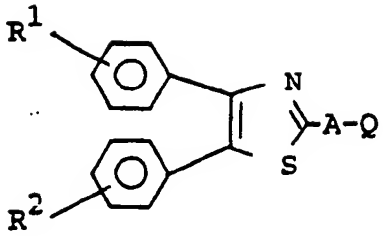
Process ①



(IV)

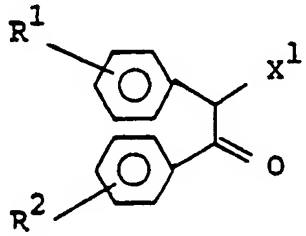


(IIa)

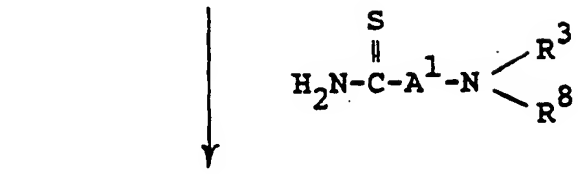


(II)

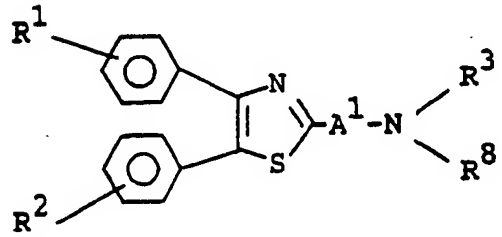
Process (2)



(IV)



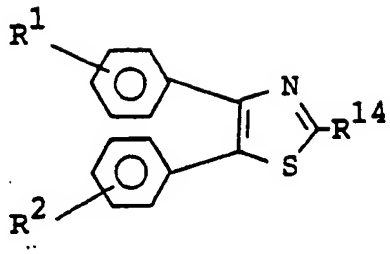
(VIa)



(VI)

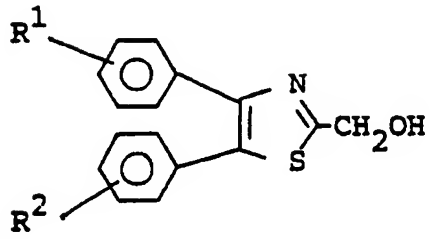
or a salt thereof

Process (3)



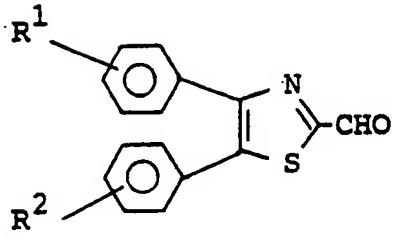
(IXa)

reduction



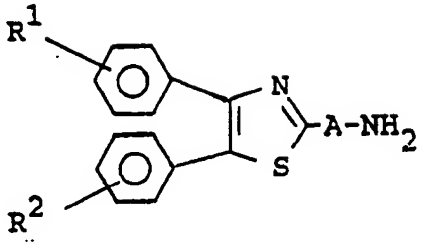
(IXb)

oxidation



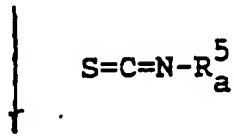
(IX)

Process (4)

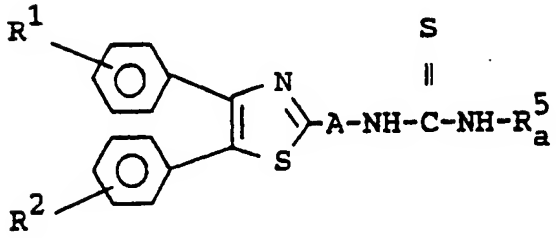


(Ib)

or a salt thereof

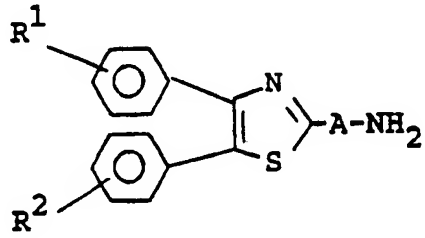


(XIIa)



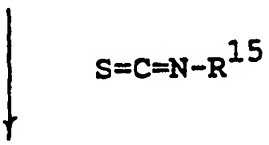
(XII)

Process (5)

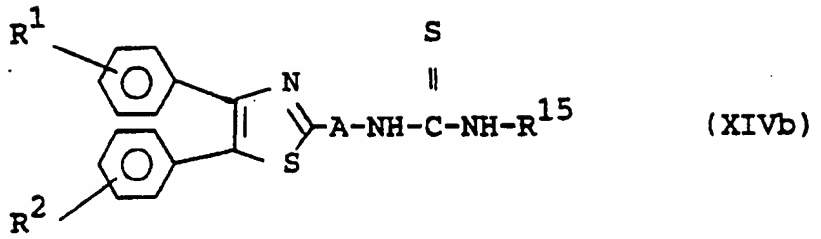


(Ib)

or a salt thereof

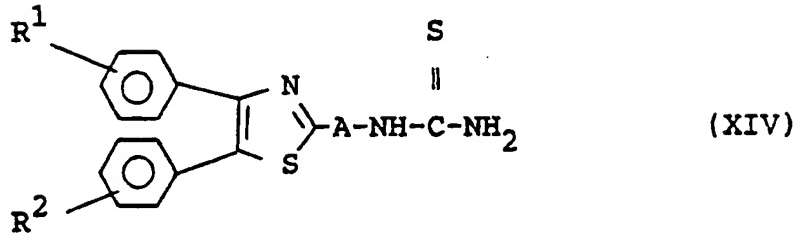


(XIVa)



(XIVb)

elimination reaction



(XIV)

wherein
R^1, R^2, R^3, R^8, R_a^5, A, A^1, Q and X^1 are each as defined above,
R^{14} is esterified carboxy such as those exemplified before and
R^{15} is acyl such as those exemplified before, preferably lower alkanoyl (e.g. acetyl, etc.) or aroyl (e.g. benzoyl, etc.).

Processes ① to ⑤ for the preparation of the starting compounds are explained in detail in the following.

Process ①

The compound (II) can be prepared by reacting the compound (IV) with the compound (IIa).

This reaction can be carried out in a similar manner to that of the aforementioned Process (b), and therefore the reaction conditions (e.g. base, solvent, temperature, etc.) can be referred to those of Process (b).

Process ②

The compound (VI) or a salt thereof can be prepared by reacting the compound (IV) with the compound (VIa). This reaction can be carried out in a similar manner to that of the aforementioned Process (b), and therefore the reaction conditions (e.g. solvent, temperature, base, etc.) can be referred to those of Process (b).

Process ③

The compound (IX) can be prepared by subjecting the compound (IXa) to a reduction, and further to an oxidation.

The said reduction can be carried out in a conventional manner by using a conventional reducing

reagent which is capable of reducing an esterified carboxy group to a hydroxy methyl group such as lithium aluminum hydride, and the like.

And the said oxidation can also be carried out in a conventional manner by using a conventional oxidizing agent which is capable of oxidizing a hydroxymethyl group to a formyl group such as manganese dioxide, and the like.

Process ④

The compound (XII) can be prepared by reacting the compound (Ib) or a salt thereof with the compound (XIIa).

This reaction can be carried out in a similar manner to that of the aforementioned Process (h), and therefore the reaction condition (e.g. solvent, temperature, base, etc.) can be referred to those of Process (h).

Process ⑤

The compound (XIV) can be prepared by reacting the compound (Ib) or a salt thereof with the compound (XIVa), and further by subjecting the resulting compound (XIVb) to an elimination reaction of the acyl group in R^{15}, in a similar manner to that of the afore-mentioned Process (c).

The first and second steps of this process can be carried out in similar manners to Processes (h) and (c), respectively, and therefore the reaction conditions (e.g. solvent, temperature, etc.) can be referred to those of Processes (h) and (c).

The other starting compounds can be prepared in a similar manner to Processes ① to ⑤ or a conventional manner.

The new thiazole compounds (I) and a pharmaceutically acceptable salt thereof of the present invention possess strong antithrombotic activity inhibiting the activities against cyclooxygenase, thrombin, and the like, and/or inhibiting aggregation of platelet; vasodilating activity; anti-allergic activity; anti-inflammatory activity; and 5-lipoxygenase inhibitory activity; particularly antithrombotic activity, and therefore are useful as antithrombotic agent, vasodilating agent, anti-allergic agent, anti-inflammatory agent and 5-lipoxygenase inhibiting agent, particularly antithrombotic agent.

Accordingly, the new thiazole compounds (I) and a pharmaceutically acceptable salt thereof can be used for prophylactic and therapeutic treatment of cerebral thrombosis, atrophic thrombosis; coronary thrombosis; creeping thrombosis; dialation thrombosis; jumping thrombosis; mural thrombosis; placental thrombosis; platelet thrombosis; posttraumatic arterial thrombosis; thrombostasis; compression thrombosis; peripheral vascular disorders such as chronic arterial occlusion; transient ischemic attack; myocardial infarction; cerebral infarction; reocclusion after percutaneous transluminal coronary angioplasty or percutaneous transluminal coronary recanalization; arteriosclerosis; cerebiral vasospam; disseminated intravascular coagulopathy; hypertension such as pulmonary hypertension; asthma; psoriasis; hepatitis; pancreatitis; arthritis; nephritis; inflammatory bowel diseases; septic shock; rhinitis; conjunctivitis; epidermitis; rheumatism; peptic ulcer; gout; dysmnesia; senile dementia; Crohn's disease; adult respiratory disease syndrome; endotoxin shock; and the like.

And, these compounds are also useful for inhibition of thrombosis during extracorporeal circulation such as dialysis.

Further, these compounds are also expected to have antipyretic activity, analgesic activity, antiviral activity, antifungal activity, and the like.

The thiazole compounds (I) and a pharmaceutically acceptable salt thereof scarcely have side effect exerting a bad influence upon patients.

In order to show the utilities of the thiazole compounds (I) and a pharmaceutically acceptable salt thereof of the present invention, pharmacological test data of the representative compound of the thiazole compounds (I) are illustrated in the following.

The expressions of "Example 1", "Example 3", "Example 5", "Example 12", "Example 14" and "Example 21" in the following tests mean the compounds prepared in Examples 1, 3, 5, 12, 14 and 21, respectively.

Platelet aggregation ex vivo (1)